# PATENT COOPERATION TREATY

# PCT



## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference<br>239-204-WO | **FOR FURTHER ACTION** | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| International application No.<br>PCT/DK 03/00734 | International filing date *(day/month/year)*<br>30.10.2003 | Priority date *(day/month/year)*<br>01.11.2002 |
| International Patent Classification (IPC) or both national classification and IPC<br>C07D211/22 | | |
| Applicant<br>NEUROSEARCH A/S et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 30.04.2004 | 18.11.2004 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized Officer<br>Zellner, A<br>Telephone No. +49 89 2399-8078 |

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK 03/00734

## I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

**Description, Pages**

1-22 as originally filed

**Claims, Numbers**

1-13 received on 20.10.2004 with letter of 18.10.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 13

   because:

   ☒ the said international application, or the said claims Nos. 13 relate to the following subject matter which does not require an international preliminary examination (specify):

   **see separate sheet**

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-13 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | 1-13 |
| | No: | Claims | |
| Industrial applicability (IA) | Yes: | Claims | 1-12 |
| | No: | Claims | |

2. Citations and explanations

   **see separate sheet**

1. The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

   D1= WO 00/20390 A
   D2= WO 98/51668 A

2. The present application relates to piperidine derivatives and to their use in medicine.

3. The amendments filed with letter dated 18.10.2004 were found to be in accordance with the requirements of Art. 34(2)(b) PCT.

item **III**

4. For the assessment of present claim 13 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

item **V**

5. Novelty (Art. 33(2) PCT)

5.1. Document D1 relates to piperidine derivatives and the use of dimeric piperidine derivatives as dopamine and serotonine reuptake inhibitors (p. 7, l. 4-5; general formula I on p. 3-4). D1 does not disclose examples falling within th escope of amended claim 1 (ex. 39 and 41 differ in several structural aspects). The disclosure of D1 is thus not considered novelty-destroying for amended claims 1-13.

1.2. Document D2 discloses compounds which are excluded expressis verbis from present claim 1 (D2: examples 1 and 2). Presently claimed compounds differ from compounds of general formula as disclosed on p. 3 of D2 in the nature of substituent $R^3$. Novelty vis-à-vis D2 can thus be acknowledged.

2. Inventive step (Art. 33(3) PCT)

Monomeric compounds according to D1 are intermediates in the preparation of the dimeric compounds disclosed in D1. Table 1 of D1 shows the ability to inhibit the reuptake of $^3$H-DA for certain monomeric compounds. The presently claimed compounds differ therefrom in the nature of substituent $R^3$ and the substituents at the phenyl ring. Applicant could show by way of comparative data that the structural changes lead to an improvement in the ability to inhibit reuptake (test examples filed with letter dated 18.10.2004). The generic definition of D2 does not encompass compounds according to amended claim 1. The provision of compounds according to amended claim 1 can thus be considered based on an inventive step. The application meets the requirements of Art. 33(3) PCT.

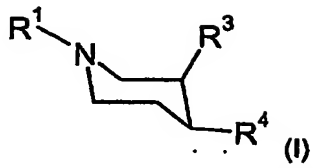
3. Industrial applicability (Art. 33(4) PCT)

Can be acknowledged for claims 1-14.

4. The description on file is not yet in accordance with the amended set of claims (Art. 6 PCT).

## CLAIMS

1. A piperidine derivative of the Formula I:



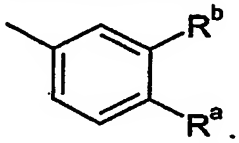
(I)

or any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof,
wherein

$R^1$ represents hydrogen or alkyl;

$R^3$ represents $-CH_2-O-R^c$;
wherein $R^c$ represents alkyl or cycloalkylalkyl;

$R^4$ represents



;
wherein $R^a$ and $R^b$ independently of each other represent halo.

2. The chemical compound of claim 1, wherein
$R^1$ represents hydrogen.

3. The chemical compound of claim 1, wherein
$R^1$ represents alkyl.

4. The chemical compound according to any one of claims 1-3, wherein
$R^c$ represents alkyl.

5. The chemical compound according to any one of claims 1-3, wherein
$R^c$ represents cycloalkylalkyl.

6. The chemical compound according to any one of claims 1-5, wherein
wherein $R^a$ represents chloro and $R^b$ represents chloro.

7. The chemical compound of claim 1, which is
1-methyl-3-ethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;

1-methyl-3-methoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
1-methyl-3-cyclopropylmethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
1-methyl-3-isobutoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
3-ethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
3-methoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
3-cyclopropylmethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
or any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof.

8. The chemical compound of claim 1, which is
(±)-Cis-1-methyl-3-ethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
(±)-Cis-1-methyl-3-methoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
(±)-Trans-1-methyl-3-ethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
(±)-Trans-1-methyl-3-methoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
(+)-Cis-1-methyl-3-ethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
(+)-Cis-1-methyl-3-methoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
(-)-Cis-1-methyl-3-methoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
(+)-Cis-1-methyl-3-cyclopropylmethoxymethyl-4- (3,4-dichlorophenyl)-piperidine;
(-)-Cis-1-methyl-3-cyclopropylmethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
(-)-Cis-1-methyl-3-isobutoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
(+)-Trans-1-methyl-3-ethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
(-)-Trans-1-methyl-3-ethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
(+)-Trans-1-methyl-3-methoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
(-)-Trans-1-methyl-3-methoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
(-)-Trans-1-methyl-3-cyclopropylmethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
(-)-Trans-1-methyl-3-isobutoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
(+)-Cis-1-methyl-3-isobutoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
(+)-Trans-1-methyl-3-isobutoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
(+)-Trans-1-methyl-3-cyclopropylmethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
(-)-Cis-1-methyl-3-ethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
(+)-Cis-3-ethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
(-)-Cis-3-ethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
(+)-Cis-3-methoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
(-)-Cis-3-methoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
(+)-Cis-3-cyclopropylmethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
(-)-Cis-3-cyclopropylmethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
(+)-Trans-3-ethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;

(-)-Trans-3-ethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
(+)-Trans-3-methoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
(-)-Trans-3-methoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
(-)-Trans-3-cyclopropylmethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
(+)-Trans-3-cyclopropylmethoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
(+)-Cis-3-isobutoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
(-)-Cis-3-isobutoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
(+)-Trans-3-isobutoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
(-)-Trans-3-isobutoxymethyl-4-(3,4-dichlorophenyl)-piperidine;
or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition, comprising a therapeutically effective amount of a compound of any one of claims 1-8, or any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

10. Use of the chemical compound of any of claims 1-8, or any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament.

11. The use according to claim 10, for the manufacture of a pharmaceutical pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to inhibition of monoamine neurotransmitter re-uptake in the central nervous system.

12. The use according to claim 11, wherein the disease, disorder or condition is mood disorder, depression, atypical depression, major depressive disorder, dysthymic disorder, bipolar disorder, bipolar I disorder, bipolar II disorder, cyclothymic disorder, mood disorder due to a general medical condition, substance-induced mood disorder, pseudodementia, Ganser's syndrome, obsessive compulsive disorder, panic disorder, panic disorder without agoraphobia, panic disorder with agoraphobia, agoraphobia without history of panic disorder, panic attack, memory deficits, memory loss, attention deficit hyperactivity disorder, obesity, anxiety, generalized anxiety disorder, eating disorder, Parkinson's disease, parkinsonism, dementia, dementia of ageing, senile dementia, Alzheimer's disease, acquired immunodeficiency syndrome dementia complex, memory dysfunction in ageing, social phobia, post-traumatic

stress disorder, acute stress disorder, drug addiction, drug misuse, cocaine abuse, nicotine abuse, tobacco abuse, alcohol addiction, alcoholism, pain, inflammatory pain, neuropathic pan, migraine pain, tension-type headache, chronic tension-type headache, pain associated with depression, fibromyalgia, arthritis, osteoarthritis, rheumatoid arthritis, back pain, cancer pain, irritable bowel pain, irritable bowel syndrome, post-operative pain, post-stroke pain, drug-induced neuropathy, diabetic neuropathy, sympathetically-maintained pain, trigeminal neuralgia, dental pain, myofacial pain, phantom-limb pain, bulimia, premenstrual syndrome, late luteal phase syndrome, post-traumatic syndrome, chronic fatigue syndrome, urinary incontinence, stress incontinence, urge incontinence, nocturnal incontinence, premature ejaculation, erectile difficulty, anorexia nervosa, sleep disorders, autism, mutism, trichotillomania, narcolepsy, post-stroke depression, stroke-induced brain damage, stroke-induced neuronal damage, or Gilles de la Tourettes disease.

13. A method for treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to inhibition of monoamine neurotransmitter re-uptake in the central nervous system, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a compound according to any one of the claims 1-8, or any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof.